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**Disposition of ^{14}C and/or ^{74}As -Cacodylic
Acid in Rats After Intravenous,
Intratracheal, or Peroral Administration**

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16. ABSTRACT

The distribution, excretion, and possible metabolism of ¹⁴C- and/or ⁷⁴As-cacodylic acid, an organoarsenical herbicide, was studied in rats following a single intravenous injection, intratracheal instillation or oral gavage. Male Sherman rats were dosed at levels ranging from 200 mg/kg to 120 µg/kg. The extent and rate of lung absorption was greater than gastrointestinal absorption. Concentrations in the liver and whole blood were higher after peroral dosing than intravenous administration. Levels observed in plasma and other tissues were similar after all three routes following the absorptive phase. The percent dose found in the whole blood, red blood cells, and plasma was similar for all doses given by these routes. Less than 0.1-1/2 of the administered dose was recovered as ¹⁴CO₂ by any route at 24 hr after administration.

Levels in all tissues decreased rapidly, but remained high in whole blood. The red blood cells were found to be the major site of body burden of cacodylic acid.

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Disposition of ^{14}C and/or ^{74}As -Cacodylic Acid in Rats after Intravenous, Intratracheal, or Peroral Administration

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The distribution, excretion, and possible metabolism of ^{14}C - and/or ^{74}As -cacodylic acid, an organoarsenical herbicide, was studied in rats following a single intravenous injection, intratracheal instillation or oral gavage. Male Sherman rats were dosed at levels ranging from 200 mg/kg to 120 $\mu\text{g/kg}$. The extent and rate of lung absorption was greater than gastrointestinal absorption. Concentrations in the liver and whole blood were higher after peroral dosing than intravenous administration. Levels observed in plasma and other tissues were similar after all three routes following the absorptive phase. The percent dose found in the whole blood, red blood cells, and plasma was similar for all doses given by these routes. Less than 0.1% of the administered dose was recovered as $^{14}\text{CO}_2$ by any route at 24 hr after administration. Twenty-four hours after intravenous, intratracheal, and peroral administration, 71, 60, and 25%, respectively, was excreted in the urine. After intravenous administration of 200 mg/kg, sufficient ^{14}C -cacodylic acid was recovered in bile to account for the small amount excreted in the feces. Cacodylic acid is probably not metabolized to inorganic arsenic since the disposition of ^{14}C and ^{74}As -cacodylic acid were identical.

Kinetic analyses of the plasma curve for ^{14}C -cacodylic acid (high dose) yielded three half-times; 0.014, 0.214 and 3.42 hr with an apparent volume of distribution of 15.3 ml. Highest initial concentrations were found in the whole blood, muscle, kidney, liver and lung.

Levels in all tissues decreased rapidly, but remained high in whole blood. The red blood cells were found to be the major site of body burden of cacodylic acid.

Introduction

The organoarsenical compound cacodylic acid (dimethylarsenic acid) is a nonselective herbicide used for control of weeds in noncrop areas, for cotton defoliation, for control of hardwood trees, and for suppression of bark beetles. Although the compound has been known for over 130 yr (1), it was introduced into use as a herbicide only in 1958.

A number of studies are available on the acute, subacute, and long-term toxicity of cacodylic acid to laboratory (2, 3) and domestic animals (4), and use experience has provided information on its hazard for man (5). Little information, however, has been published on the pharmacodynamic aspects of exposure in experimental animals or man for either cacodylic acid or the closely related monosodium methanearsenate (MSMA) and disodium methanearsenate (DSMA).

This paper describes studies on the absorption, distribution, storage, metabolism, and excretion of radiolabeled cacodylic acid in rats. Routes of exposure used include intravenous injection, intratracheal instillation, and oral gavage.

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Methods

Young male Sherman strain rats were obtained from the Center for Disease Control, Atlanta, Georgia, and allowed to acclimatize in our animal quarters. Rats used in the study were determined to have normal weight gain and urinalysis [Combistix, Ames]. The rats weighed 280–380 g and were not fasted before treatment. Time-pregnant CD rats (Charles Rivers, Inc.), were used in the placental transfer studies. ^{14}C - and ^{74}As - (half-life = 18 days) labeled cacodylic acid was synthesized by ICN Pharmaceuticals, Inc., Irvine, California. For the dual label experiments, aliquots of the ^{14}C - and ^{74}As -cacodylic acid were mixed. The specific activity of the ^{14}C - and ^{74}As -cacodylic acid was 10 mCi/mmol and 2 mCi/mmol, respectively. The radiochemical purity was reported and confirmed to be 99% by autoradiographic thin-layer chromatography.

Lung absorption of ^{14}C -cacodylic acid was determined after the method of Enna and Schanker (6). A PE 240 cannula was inserted as a guide between the fourth and fifth tracheal ring of chloral hydrate anesthetized rats to a depth of 6 mm. Dosing was accomplished through a smaller rubber cannula permitting passage only to the bifurcation of the trachea. A 100 μl portion of solution was administered for a dose of 78 mg/kg. The lungs and trachea were removed at 0, 5, 10, and 20 min and assayed for the amount of ^{14}C -cacodylic equivalents remaining.

Peroral absorption kinetics were estimated by sacrificing 4 hr after administration and counting the entire gastrointestinal tract for percent of dose remaining.

For the intravenous and oral high dose studies, cacodylic acid (Fisher Scientific Co., 95% cacodylic acid and 5% water) at a concentration of 60 mg/ml and labeled with ^{14}C -cacodylic acid to an activity of 530 $\mu\text{Ci/ml}$ was used.

Rats were dosed intravenously with 200 mg/kg (0.5 ml/150 g body weight) via the tail vein and sacrificed at 0.117, 0.25, 1.0, 24, and 72 hr after administration. The concentration of ^{14}C -cacodylic acid-equivalent was assayed in blood, lung, liver, brain, spleen, and kidney. Additional animals were dosed similarly for the blood clearance. Whole blood was collected at selected intervals from the intraorbital sinus in a 50 μl heparinized capillary tube. The sample was then centrifuged in a microhematocrit centrifuge, the hematocrit determined, and the sample divided into plasma and red blood cells by severing the capillary tube by use of a diamond glass scribe. The plasma and cells were then processed for counting.

Biliary secretion was measured in pentobarbital anesthetized rats by cannulating the common bile duct with PE 10 tubing and collecting quantitatively the biliary secretion in microcapillary tubes for assay.

Intratracheally instilled rats were given 0.1 ml/150 g of body weight of ^{14}C -cacodylic acid for a dose of 200 mg/kg (53 $\mu\text{Ci/ml}$). Rats were anesthetized with ether or 0.5 ml of chloral hydrate (200 mg/kg) and a catheter (approximately 3 cm) with an internal diameter of 1.68 mm positioned surgically. Animals were allowed to recover from anesthesia and dosed by using a cannula with an external diameter of 1.09 mm to allow breathing during dosing. The cannula was inserted approximately 5 cm to the tracheal bifurcation. Whole blood was collected from the intraorbital sinus as described previously. All tissues and fluids were digested in 2 ml of NCS Biological Solubilizer (Amersham/Searle), 15 ml of scintillation counting fluid added, and counted (Mark III/Searle Analytic Inc.).

Additional animals were dosed by the three routes and placed in animal containment chambers (Plas-Labs, Lansing, Michigan) and all effluent was passed through Carbo-sorb II (Packard) for $^{14}\text{CO}_2$ collection.

For low dose administration, adult Sherman and CD rats were given a fixed volume of 0.5 ml of aqueous solution containing 33 μg of ^{14}C -cacodylic acid and amounts of ^{74}As -cacodylic acid ranging from 3.47 to 13.88 μg . It was necessary to adjust the amount of ^{74}As -cacodylic acid because of its short half-life. The dose was given intravenously via the tail vein, intratracheally or perorally. Intratracheal installation was done in methohexital anesthetized animals. The administration was facilitated with an 18 gauge needle guided to the tracheal bifurcation while using an otoscope light source.

The following tissues were taken at selected times post administration: blood, heart, lung, spleen, kidney, liver, brain, testes and femoral muscle. Tissues were homogenized in 4 volumes of 0.85% saline per gram of tissue by using a Polytron homogenizer. A 250 μl aliquot sample was taken and digested in 1 ml of NCS (12 hr). Whole blood was collected in a 10 ml heparinized Vacutainer (Becton-Dickinson) from the abdominal aorta unless otherwise specified. Plasma and red blood cells were also harvested.

Both ^{14}C and ^{74}As isotopes were counted by using Beta counting techniques. ^{14}C was evaluated at a 200 keV energy level and ^{74}As at 700 keV energy level. ^{14}C had a counting efficiency of 63% in the dual isotope program used. A theoretical efficiency of ^{74}As of 38% was calculated based on the specific activity of ^{74}As on the day of shipment

from the supplier. Quench curves were constructed for the two isotopes individually and in combination. Any spillover in energy levels were considered. Known standards were run daily to correct for decay of ^{74}As label. Radioarsenic was also determined by gamma spectrometry with an Auto-Gamma Scintillation Spectrometer (model 5986) and a Armac Scintillation Spectrometer (Packard Instrument Co.).

Whole blood volume and muscle mass was estimated by using published procedures: $0.055 \times$ body weight^{0.99} (7), and $0.45 \times$ body weight, respectively (8). Plasma volumes were estimated from hematocrit values and the whole blood volume.

Results

The results of studies to determine lung and gastrointestinal absorption in the rat are shown in Figure 1. It can be seen that cacodylic acid is rapidly absorbed from the rat lung, with less than 5% remaining at 15 min. The half-time for absorption from the lung was found to be 2.2 min. The estimated half-time for peroral absorption was found to be 248 min.

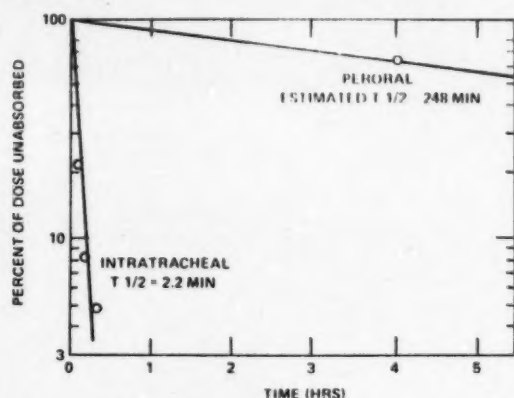


FIGURE 1. Pulmonary absorption of 78 mg/kg of ^{14}C -cacodylic acid and gastrointestinal absorption of 33 μg of ^{14}C - and 6.9 μg of ^{74}As -cacodylic acid by male Sherman rats.

The mean intravenous plasma ^{14}C -cacodylic acid (200 mg/kg) data (Fig. 2) were analyzed for decay constants and intercepts by nonlinear least squares techniques on a digital computer. This procedure yielded a three-exponential equation with half-times of 0.014 hr, 0.217 hr and 3.42 hr and an apparent volume of distribution of 15.3 ml.

Figure 3 characterizes the plasma curves for the administration of 33 μg of ^{14}C -cacodylic acid by the intravenous, intratracheal, and peroral routes. The maximal concentration after intratracheal administration was seen at 5 and 10 min, and similar curves

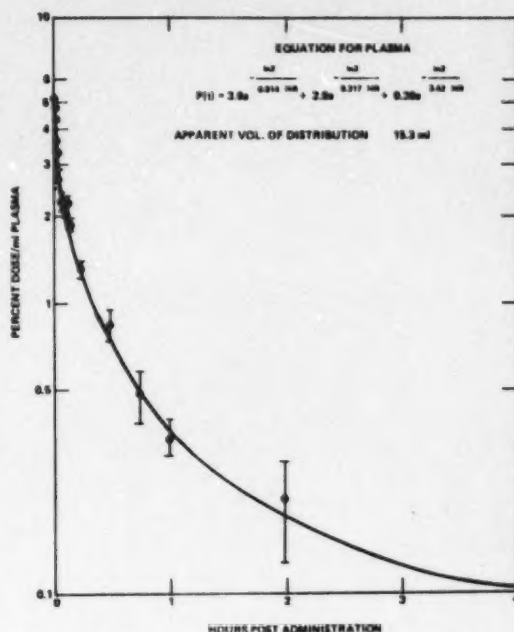


FIGURE 2. Kinetic analysis of the plasma curve obtained after the administration of 200 mg/kg of ^{14}C -cacodylic acid to male Sherman rats.

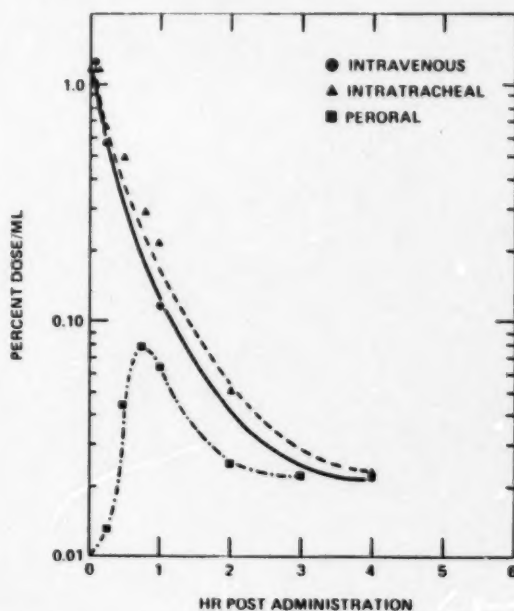


FIGURE 3. Comparison of plasma curves after (●) intravenous, (▲) intratracheal, and (■) peroral administration of 33 μg of ^{14}C -cacodylic acid and 3.5, 13.8 and 6.9 μg of ^{74}As -cacodylic acid given to male Sherman rats.

were found for intravenous and intratracheal plasma clearance. The much slower absorption from the gastrointestinal tract resulted in peak plasma levels around 1 hr. A comparison of whole blood levels after the three routes of exposure (Fig. 4) shows that higher concentrations are achieved after peroral administration and that significant pulmonary clearance and gastrointestinal absorption as reflected by the positive slope occurs after intratracheal administration (insert, Fig. 4). The clearance of cacodylic acid from the whole blood after intravenous, intratracheal and peroral administra-

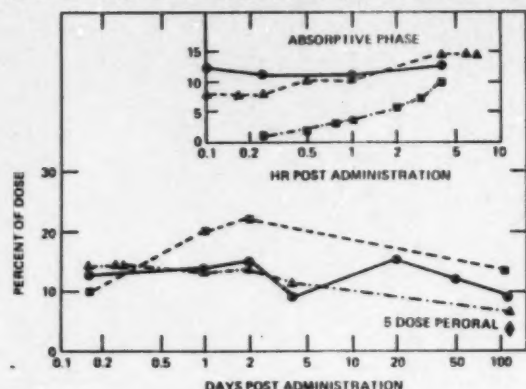


FIGURE 4. Comparison of whole blood curves after (●) intravenous, (▲) intratracheal, and (■) peroral administration of ^{14}C -cacodylic acid and 3.5, 13.8 and 6.9 μg of ^{74}As -cacodylic acid given to male Sherman rats.

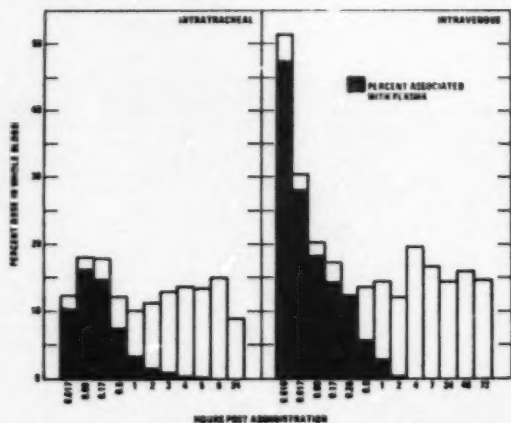


FIGURE 5. Comparison of whole blood and plasma levels after the intravenous and intratracheal administration of 200 mg/kg of ^{14}C -cacodylic acid.

Table 1. Whole blood levels 24 hr after one or five doses of cacodylic acid given peroral to male Sherman rats.

No. of doses	4s, ng/ml $\pm$ SEM ^a
1	45.2 $\pm$ 3.33
4	178 $\pm$ 13.1

^aAdministered a dose of 12.7 μg of ^{14}C -cacodylic acid and 3.4 μg of ^{74}As -cacodylic acid.

Table 2. Distribution of radiolabel after intravenous administration of cacodylic acid to adult male Sherman rats (dose comparison).

Organ	% of dose recovered			
	15 min		1 hr	
	High ^a	Low ^b	High ^a	Low ^b
Lung	0.61	0.44	0.31	0.25
Liver	9.81	5.00 ^c	1.08	1.34
Brain	0.08	0.03	0.05	0.05
Spleen	0.20	0.12	0.08	0.05
Kidneys	2.98	4.69 ^c	0.68	0.88
Whole blood	12.5	11.01	14.8	11.0

^aMean of at least three animals given 200 mg/kg ^{14}C -cacodylic acid.

^bMean of four animals given 33 μg of ^{14}C -cacodylic acid and 3.47 μg of ^{74}As -cacodylic acid.

^cDifferent at $P \leq 0.05$.

Table 3. Distribution of radiolabel after intravenous administration of ^{74}As - and ^{14}C -cacodylic acid to adult male Sherman rats (label comparison).

Organ	Radio label ^a	% of dose recovered/tissue			
		5 min	4 hr	48 hr	60 days
Heart	^{14}C	0.24	0.06	0.06	0.03
	^{74}As	0.23	0.08	0.07	0.04
Lung	^{14}C	0.73	0.21	0.23	0.09
	^{74}As	0.60	0.19	0.19	0.11
Spleen	^{14}C	0.13	0.12	0.08	0.05
	^{74}As	0.10	0.10	0.10	0.05
Kidneys	^{14}C	7.69	0.13	0.12	0.05
	^{74}As	8.36	0.12	0.10	0.09
Liver	^{14}C	6.32	0.55	0.58	0.23
	^{74}As	6.90	0.54	0.50	0.15
Testes	^{14}C	0.39	0.06	0.03	0.01
	^{74}As	0.41	0.06	0.03	0.02
Muscle	^{14}C	12.8	1.58	1.31	0.44
	^{74}As	14.3	1.23	1.33	0.37

^aRats were given 11.6 mCi of ^{14}C (33 μg of cacodylic acid) and 5 mCi of ^{74}As (3.47 μg of cacodylic acid); ^{14}C measured by beta emission; ^{74}As , by gamma emission.

Table 4. Distribution of ^{14}C -cacodylic acid and/or its metabolites in certain organs of male Sherman rats after intravenous administration.

Organ	% of dose recovered				
	1 min	15 min	1 hr	72 hr	168 hr
Lung	1.86 ^a	0.61	0.31	0.22	0.13
Liver	1.97	9.81	1.08	0.33	0.30
Brain	0.18	0.08	0.08	0.05	0.02
Spleen	0.19	0.20	0.15	0.08	0.05
Kidney	2.23	2.98	0.68	0.05	0.07
Whole blood	30.5	12.5	14.7	14.8	9.9

^aMean of at least three animals given 200 mg/kg ^{14}C -cacodylic acid (8.8 $\mu\text{Ci}/\text{mg}$).

Table 5. Tissue distribution of radiolabel 105 days after the administration of ^{14}C -cacodylic acid to adult male Sherman rats (route comparison).^a

Tissue	ng/g		
	Intravenous	Intratracheal	Peroral
Heart	4.86 $\pm$ 1.55 (0.02) ^b	7.39 $\pm$ 1.70 (0.02)	8.47 $\pm$ 1.33 (0.05)
Lung	16.8 $\pm$ 1.22 (0.09)	20.2 $\pm$ 5.40 (0.07)	24.8 $\pm$ 5.93 (0.11)
Spleen	15.8 $\pm$ 2.87 (0.03)	41.2 $\pm$ 7.81 ^c (0.07)	31.5 $\pm$ 7.87 (0.06)
Liver	5.86 $\pm$ 0.66 (0.19)	5.58 $\pm$ 2.56 (0.29)	15.7 $\pm$ 5.69 (0.54)
Kidney	5.75 $\pm$ 0.33 (0.04)	13.9 $\pm$ 2.70 ^c (0.08)	9.68 $\pm$ 1.82 (0.07)
Brain	1.66 $\pm$ 0.22 (0.01)	2.84 $\pm$ 1.28 (0.01)	1.82 $\pm$ 0.48 (0.01)
Testes	1.22 $\pm$ 0.22 (0.02)	1.28 $\pm$ 0.14 (0.01)	1.69 $\pm$ 0.12 (0.02)
Muscle	0.88 $\pm$ 0.22 (0.47)	0.85 $\pm$ 0.28 (0.33)	0.85 $\pm$ 0.36 (0.45)

^aAll animals given a single 33 μg dose of ^{14}C -cacodylic acid with 3.5 μg intravenously, 13.8 μg intratracheally, and 6.9 μg perorally of ^{74}As -cacodylic acid.

^bMean percent of total dose per tissue parenthesis ($N = 4$).

^cDifference from intravenous dose at $p < 0.05$.

tion displayed half-times of approximately 92, 76, and 90 days, respectively. It should be noted that higher blood levels were achieved after a single peroral dose than similar dosing by other routes although five consecutive daily peroral doses resulted in lower blood levels at 105 days.

Comparison of whole blood levels 24 hr after one and four daily peroral doses (Table 1) indicates linear accumulation of ^{14}C -label after multiple dosing (3.9 times the single dose).

Data which compare whole blood and plasma distribution after intravenous and intratracheal instillation (200 mg/kg) are presented in Figure 5. Although cacodylic acid is retained by the whole blood, it is rapidly eliminated from the plasma.

Since the plasma and whole blood data that have been presented were obtained after different levels of dosing, it is important to consider the matter of dose dependency. The data given in Table 2 address this issue. It can be seen that, with the exception of differences observed in levels in the liver and kidney at 15 min, no significant differences in the percent dose recovered in tissues or whole blood was observed after the administration of different dose levels. Data given in Table 3 indicate no significant differences in distribution after intravenous dosing in ^{14}C - or ^{74}As -labeled cacodylic acid.

The distribution of ^{14}C -cacodylic acid (200 mg/kg) given intravenously is shown in Table 4. Despite a rapid decline in tissue levels, whole blood tends to retain the ^{14}C -label.

Although differences in whole blood levels after intravenous, intratracheal and peroral dosing were noted at 105 days (Fig. 4), only three differences were noted in tissue levels at this time (Table 5). The level of ^{14}C -label in the spleen and kidney were higher after intratracheal instillation than after intravenous and higher levels were observed in the

liver after peroral dosing when compared to intravenous.

The results presented in Table 6 indicate that three tissues, the spleen, kidney, and brain, have higher levels of ^{14}C -label after multiple oral dosing.

Elimination and retention of cacodylic acid is shown in Table 7. More cacodylic acid is retained after peroral administration than either intravenous or intratracheal. The primary route of excretion after peroral dosing was fecal. Urinary excretion was lower after peroral dosing when compared with other routes.

The demethylation of ^{14}C -cacodylic acid was evaluated. These results (Table 8) show that only a small fraction of the dose was evolved as $^{14}\text{CO}_2$. It should be noted that an approximately 10-fold higher level of $^{14}\text{CO}_2$ is eliminated by the peroral route when compared to other routes.

Approximately 1% of the dose administered intravenously was eliminated in the feces (Table 7).

Table 6. Tissue distribution of radiolabel 105 days after a single dose or five doses of cacodylic acid perorally (number of dose comparison).

Tissue	% of doses/organ	
	Single dose ^a	Five doses ^b
Heart	0.05 (0.03-0.10) ^c	0.08 (0.29-0.09)
Lung	0.11 (0.09-0.18)	0.13 (0.09-0.19)
Spleen	0.06 (0.03-0.10)	0.12 (0.11-0.14) ^c
Liver	0.54 (0.23-1.17)	0.53 (0.11-0.58)
Kidney	0.07 (0.04-0.08)	0.17 (0.11-0.18) ^d
Brain	0.01 (0.01-0.02)	0.02 (0.02-0.04) ^d
Testes	0.02 (0.01-0.02)	0.02 (0.02-0.03)
Muscle	0.45 (0.24-0.86)	0.55 (0.44-0.78)

^aRats given 33 μg of ^{14}C -cacodylic acid and 6.9 μg of ^{74}As -cacodylic acid.

^bRats given 12.7 μg of ^{14}C -cacodylic acid and 3.4 μg of ^{74}As -cacodylic acid (times 5).

^cMean (range); $N = 4$.

^dDifferent at $p < 0.05$.

Table 7. Retention and excretion of cacodylic acid at 24 hr.

Route	Percent of dose				
	Whole body	Urine	Feces	Total	% Absorbed
Intravenous ^a	20.5 (16.1-26.9)	70.9 (57.7-80.2)	1.18 (0.2-2.9)	92.6	100
Oral ^b	31.8 (25.0-46.4)	25.2 (20.1-28.7)	31.1 (27.4-36.9)	88.1	66
Intracheal ^c	24.3 (16.7-31.7)	60.0 (43.2-78.3)	8.32 (3.9-14.1)	92.6	92

^aRats given 33 μ g of ¹⁴C-cacodylic acid and 3.5 μ g of ⁷⁴As-cacodylic acid.

^bRats given 33 μ g of ¹⁴C-cacodylic acid and 6.9 μ g of ⁷⁴As-cacodylic acid.

^cRats given 33 μ g of ¹⁴C-cacodylic acid and 13.8 μ g of ⁷⁴As-cacodylic acid.

Table 8. Elimination of ¹⁴C-cacodylic acid as ¹⁴C-CO₂ after intravenous, intratracheal, and peroral administration to male rats.

Sampling times after dosing, hr	Cumulative % of dose ^a		
	Intravenous	Intracheal	Peroral
0.5	2.9×10^{-3}	1.1×10^{-3}	1.5×10^{-2}
1	2.9×10^{-3}	3.7×10^{-3}	4.1×10^{-2}
2	4.4×10^{-3}	5.2×10^{-3}	4.9×10^{-2}
4	7.2×10^{-3}	6.9×10^{-3}	6.2×10^{-2}
24	7.9×10^{-3}	^b	13×10^{-2}

^aRats given 200 mg/kg of ¹⁴C-cacodylic acid by all routes.

^bSample not taken.

Experiments indicate that cacodylic acid is excreted in the bile (Table 9).

All the data previously presented were obtained using the male Sherman rat as the model. Comparison of male and female rat tissue distribution of cacodylic acid at 1 and 72 hr after a single intravenous dose indicate no sex-related differences in concentration (Table 10).

Table 9. Biliary secretion of ¹⁴C-cacodylic acid after intravenous dosage (200 mg/kg).

Time of collection, hr	Average volume, ml $\pm$ error	Average secreted, μ g $\pm$ error ^a	Cumulative % of dose
0.25	0.22 ± 0.02	0.38 ± 0.05	0.057
0.5	0.25 ± 0.03	0.38 ± 0.01	0.114
1	0.32 ± 0.03	0.31 ± 0.01	0.161
2	0.54 ± 0.07	0.44 ± 0.10	0.226

^aTwo rats anesthetized with 50 mg of pentobarbital; common bile duct cannulated with PE 10 tubing.

Table 10. Distribution of radiolabel after administration of 200 mg/kg ¹⁴C-cacodylic acid to adult Sherman rats (sex comparison).

Avg. dose mg/SEM	Time post dosing, hr	Tissues, μ g equivalents/g $\pm$ SEM					
		Sex	Liver	Lung	Brain	Spleen	Kidneys
34 $\pm$ 2	1	Male	47 $\pm$ 3 (1.1) ^a	89 $\pm$ 19 (0.26)	14 $\pm$ 3 (0.07)	70 $\pm$ 16 (0.15)	144 $\pm$ 13 (0.68)
25 $\pm$ 2	1	Female	61 $\pm$ 6 (1.3)	93 $\pm$ 9 (0.28)	16 $\pm$ 2 (0.10)	77 $\pm$ 1 (0.14)	122 $\pm$ 7 (0.52)
32 $\pm$ 3	72	Male	16 $\pm$ 2 (0.36)	74 $\pm$ 5 (0.24)	11 $\pm$ 4 (0.06)	53 $\pm$ 2 (0.09)	12 $\pm$ 2 (0.06)
24 $\pm$ 1	72	Female	14 $\pm$ 1 (0.33)	68 $\pm$ 6 (0.25)	11 $\pm$ 1 (0.07)	61 $\pm$ 3 (0.10)	15 $\pm$ 1 (0.07)

^aNumbers in parentheses equals denote percent of dose/organ; mean of four animals given 200 mg/kg of ¹⁴C-cacodylic acid.

Cacodylic acid readily crosses the placenta (Table 11) 24 hr prior to parturition. Levels obtained in the whole blood of the fetus were not different than the maternal levels. Comparison with maternal tissue levels indicate differences in fetal tissue concentrations for brain and kidney but not liver.

Discussion

Cacodylic acid is absorbed from the rat lung and gastrointestinal tract. Plasma and whole blood curves obtained after intratracheal instillation are similar to those obtained after intravenous administration. The slower absorption of cacodylic acid after peroral administration is reflected in plasma and whole blood data. The estimated gastrointestinal half-time of 248 min agrees well with the 209 minute value reported by Hwang and Schanker (9). The absorption after peroral and intratracheal administration was 66 and 92%, respectively.

Cacodylic acid has a high affinity for the rat erythrocyte as evidenced by the rapid transfer from the serum fraction and the retention in the whole blood. It is well established that the rat differs from other tested species in its erythrocyte affinity for inorganic arsenic (8, 10). The data presented in this study indicate a half-time of 90 days, which agrees well with the mean life of rat red blood cell (8).

Despite the fact that single dose peroral administration leads to higher whole blood levels than intra-

Table 11. Distribution of radiolabel 24 hr after the administration of ^{74}As and ^{14}C -cacodylic acid to adult pregnant CD-1 rat on day 21 of gestation (placental transfer).

Fluid or tissue	Maternal, ng/ml or ng/g ^a	Fetal, ng/ml or ng/g
Whole blood	228 $\pm$ 24	192 $\pm$ 31
Brain	2.76 $\pm$ 24	1.21 $\pm$ 0.11 ^b
Kidney	1.2 $\pm$ 2.06	2.46 $\pm$ 0.29 ^b
Liver	19.17 $\pm$ 2.28	16.9 $\pm$ 1.78
Urine	21170 $\pm$ 720 (64.2) ^c	

^aSince no difference was observed between percent ^{74}As and ^{14}C -cacodylic acid only ^{14}C data are given; mean of five values $\pm$ SEM (litters taken as a unit) ng equivalents after 33 μg dose of ^{14}C -cacodylic acid and 3.5 μg of ^{74}As -cacodylic acid.

^bDifferent at $P > 0.05$.

^cAs equivalents excreted in 24 hr $\pm$ SEM (% of dose).

tracheal and intravenous dosing and the administration of five daily doses produces whole blood levels four times as high as a single dose, at 105 days the percent of dose remaining in the whole blood after five daily peroral doses was less than that after a single dose by other routes. The total amount of cacodylic acid administered with the multiple dosing was approximately 80 μg compared to 40 μg given in a single dose. It is unlikely that reduced retention by the erythrocytes is related to absorption or cellular damage.

Cacodylic acid does not appear to be converted from organic to inorganic arsenical since the tissue distribution of ^{74}As - and ^{14}C -labeled cacodylic acid were not different. The present experimental results do not exclude possible changes in the valence states of the arsenic however.

High transient levels of cacodylic acid were found in muscle, kidneys, liver and lung. Lanz et al. (8) observed a similar distribution after administering carrier-free ^{74}As . At 105 days after a single dose, detectable levels of cacodylic acid were found in all tissues evaluated. Highest concentrations were found in the lung and spleen. More radiolabel was recovered in the spleen and kidney of rats given cacodylic acid intratracheally than intravenously. More cacodylic acid was found in the liver of perorally dosed rats than those treated intravenously. The reasons for these differences are not understood at this time.

Despite lower whole blood levels found at 105 days after multiple oral dosing as compared to a single dose, a higher percent of the dose was re-

covered in the spleens, kidneys and brains after multiple dosing.

The excretion of cacodylic acid was very rapid, with more than 60% of the dose being excreted in the urine after intravenous and intratracheal administration and only minor amounts being excreted in the feces while after peroral dosing 25% of the dose was recovered in the urine and 31% in the feces. Secretion of the arsenical into the bile explains the small amount found in the feces after intravenous administration. Only minor amounts of label were evolved as $^{14}\text{CO}_2$.

Studies did not indicate any sex-related differences in the distribution of cacodylic acid. It was also found that cacodylic acid can pass the placental barrier just prior to parturition, achieving levels in the whole blood of the fetus comparable to the maternal animal.

Mention of commercial products does not imply endorsement by the United States Environmental Protection Agency.

REFERENCES

1. Bunsen, R. Untersuchungen über die Kakodylreihe, *Ann. Chem.*, 46: 1 (1843).
2. Nees, P. O. Report on cacodylic acid toxicity to animals, Wisconsin Alumni Research Foundation, EPA Pesticide Petition No. OF0911 (1960). Cited in Initial Scientific Review of Cacodylic Acid, EPA-540/1-75-021 Dec. 1975.
3. Innes, J. R. M., et al. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42: 1101 (1969).
4. Peoples, S. A. Toxicity of cacodylic acid to animals. University of California, School of Veterinary Science, EPA Pesticide Petition No. OF0911 (1963). Cited in Initial Scientific Review of Cacodylic Acid, EPA-540/1-75-021 Dec. 1975.
5. Tarrant, R. F., and Allard, J. Arsenic levels in urine of forest workers applying silvicides. *Arch. Environ. Health*, 24: 277 (1972).
6. Enna, S. J., and Schanker, L. S. Absorption of drugs from the rat lung. *Am. J. Physiol.* 222: 409 (1972).
7. Spector, W. S., Ed. Handbook of Biological Data, USAF, Wright Patterson Air Force Base, Ohio, 1957, p. 355.
8. Lanz, H., Jr., Wallace, P. C., and Hamilton, J. G. The metabolism of arsenic in laboratory animals using ^{74}As as a tracer. *University of Calif. Publ. Pharmacol.* 2: 263 (1950).
9. Hwang, S. W., and Schanker, L. S. Absorption of organic arsenical compounds from the rat small intestine. *Xenobiotica* 3: 351 (1973).
10. Hunter, F. T., Kip, A. F., and Irvine, J. W., Jr. Radioactive tracer studies on arsenic injected as potassium arsenite. *J. Pharmacol. Exptl. Therap.* 76: 207 (1942).

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